

REMARKS

Claims 1 and 3-46 are pending in the present application. Claims 18 - 29 stand withdrawn from consideration. Reconsideration is respectfully requested.

Applicants' representative wishes to thank Examiner's Lau and Jiang for the helpful and courteous interview of March 5, 2009. As a result of the discussion, it is believed that the issues in the case have been clarified and that the prosecution of the application has been materially advanced.

Specification Amendments

The specification has been amended on page 51 in order to correct the spelling of the term "photolytic." The correction does not present new matter into the case. Entry of the amendment is respectfully requested.

Claim Amendments

Applicants have voluntarily deleted the limitation of a substituted alkyl having up to 4 carbon atoms and a substituted alkoxy having up to 4 carbon atoms from Claim 1 and Claim 30.

Claim Rejection, 35 USC 112, 1st Paragraph

The Examiner continues to insist that the specification contains a number of terms in describing the invention that do not reasonably convey to one of skill in the art sufficient meaning as to enable the skilled artisan to practice the invention. Applicants reiterate that all of the terms that have been used in the specification are very familiar to the skilled artisan, and as such would have no difficulty in practicing the invention as claimed.

As to the term “substituted” those of skill in organic chemistry and molecular biology are well aware of the specific types of groups would constitute suitable substituents. In Claim 1, in view of the elimination of the term “substituted” as a modifier of “alkyl” and “alkoxy,” the term remains as a modifier for the terms “aryl” and “hetaryl.” In this case the disclosure at the top of page 12 specifically discloses the terms “alkyl,” “alkoxy,” “halogen,” “hydroxyl,” “amino,” “acyl,” “nitro,” “cyano,” and “thioalkyl.” as groups for substitution on “aryl” and “heteroalkyl.” Thus, there is no problem of a sufficiency of disclosure of substituent groups on for these two types of aromatic groups. The point remains, the term “substituted” connotes a well known meaning to those of skill in the art.

With regard to the term “leaving group,” this term is defined on page 12 of the text. Further discussion of the term is found in the first paragraph of page 16, leaving no doubt to the skilled artisan of what kind of groups the term embraces.

As to “photolabile protective groups,” clearly the meaning of such is well known in light of, for instance, the disclosure of the Pfleiderer et al patent which describes precisely nucleoside derivatives that contain photolabile protective groups. The skilled artisan obviously knows what is meant by the term of photolability.

“Functional groups which are useful in oligonucleotide synthesis” the specification exactly describes such functional groups on page 16, lines 20-25 of the text, as well as in other places.

“Protective groups useful in oligonucleotide synthesis” are also discussed in the first full paragraph of page 17 of the text. One of skill in the art from this disclosure surely knows what types of groups would be useful as protective groups, particularly in the event of OH substitution which can be protected, for instance, in the form of an ester or perhaps even a carbonate. Page 17 of the text also contains a discussion of the term “modifications” which again leaves no doubt as to the enablement provided by the text to the skilled artisan.

Applicants also refer to the paragraph at page 12, lines 17-21 of the specification and to the paragraph bridging pages 12 and 13 for an adequate description of what is meant by the terms “modifications” and “nucleoside analog.” Again, one of skill in the art, from the description provided, is enabled by the text as to what is meant by the indicated terms. One of skill in the art has an understanding of what these terms mean.

Applicants do not agree with the Examiner that in order to provide an enabling text, applicants need to provide genus/species disclosure of various groups or components of the nucleoside and nucleotide molecules in order to provide an enabling disclosure of the invention to one of skill in the art. Applicants, in fact, maintain that one of skill in the art already knows the meanings of the terms questioned by the Examiner even before he/she takes the text that describes the present invention in hand. Applicants also suggest consideration of the publication by Greene et al, Protective Groups in Organic Synthesis 2d, John Wiley and Sons (1991) which is cited on page 11 of the present specification.

Claim Rejection, 35 USC 112, 2nd Paragraph

Applicants refer to the discussion above concerning the meaning of the various terms found in the claims that correspond to the terms as used in the specification. It is maintained that one of skill in the art is well aware of what types of groups qualify as substituents for groups R¹ and R² in the claims. One of ordinary skill in the art is well aware of what substituent groups are useful for the organic radicals which constitute R¹ and R².

With respect to Claim 13, one of skill would recognize that useful OH protecting groups could include the likes of ester and carbonate groups. There is nothing indefinite or lacking clarity in the terms questioned by the Examiner that are used in the claims. Other useful protecting groups are ether groups such as permitted by Claims 13 and 14 where R⁵ is specifically dimethoxytrityl and monomethoxytrityl. Claim 15 permits yet another protective

group in the form of a silyloxy group. Accordingly, the indefiniteness ground of rejection is believed overcome.

Claim Rejection, 35 USC 103

Claims 1, 3, 5 and 7-17 stand rejected based on 35 U.S.C. §103(a) as obvious over Pfleiderer et al in view of Fodor et al, U.S. Patent 5,489,678. This ground of rejection is respectfully traversed.

The Examiner indicates correctly that the distinction between the invention described by Pfleiderer et al and that of the present invention resides in the fact that in Pfleiderer et al, substituent R² on the phenyl ring of the phenylpropoxycarbonyl photolabile group is hydrogen or methoxy, while group R² in the photolabile group is an aryl group, a substituted aryl group, a heteroaryl group, substituted heteroaryl group, an aroyl group, or a substituted aroyl group. Thus, there is a complete distinction between R² groups. That, in fact, this distinction is important can be ascertained by a consideration of the photolysis half-life data presented for the compounds shown in Table 1 on pages 53 and 54 of the text. Here, compounds 1-4 are deoxythymidyl derivatives protected by the photolabile radical shown in which the R² group is a phenyl substituent, and thus are within the scope of the present claims. Comparative compounds are shown as 5-7 with compound 7, in particular, being within the scope of the Pfleiderer et al patent. (Compounds 5 and 6 are other art known compounds containing photolabile radicals that are outside the scope of the invention.) The half-life photolysis data show that the compound embodiments of the present invention photolyze much faster than the other three compounds shown in the table. Applicants submit that these results would not be expected by one of skill in the art for a number of reasons which include the following four:

- (i) It is very essential how the substituents have an influence on the extinction of the whole or complete nucleoside derivative.
- (ii) How electron transfer occurs depends on the nature of the substituents on the phenyl ring. For example, alkoxy groups were considered favorably since they transfer electrons into the phenyl ring.
- (iii) Steric effects play an important role with regard to the photolytic cleavage of the protecting groups.
- (iv) A decisive effect for a given photolytic cleavage of a protecting group is whether the transfer of energy occurs via the triplet state or the singlet state. Generally speaking triplet energy transfer is more favorable because of the longer triplet lifetime.

To summarize, it is practically impossible to predict how a substituent on the phenyl ring will have an influence on these four effects and therefore on the photolytic cleavage of the protecting groups.

Applicants also believe that the Examiner's stated position with respect to π -conjugation is incorrect for the following reasons:

- 1) If the Examiner's theory were to be correct compounds 5 and 6 in Table 1 of the specification must show better photolysis rates in comparison to that of compound 7 because of the fact that the C=O groups of the methoxycarbonyl or t-butoxycarbonyl groups form a π -conjugated system with the unsaturation of the phenyl ring. The fact that the opposite is the case clearly shows that the Examiner's proposed theory with respect to π -conjugation is too simple and therefore not reliable.

2) If the Examiner's theory were to be correct there should be no difference if according to the present invention the second phenyl ring is in a para, meta or ortho position to the NO₂ group, since the π-conjugation of the phenyl ring occurs in every position.

The discovery of the present invention is that the phenyl ring must be in the para position relative to the nitro group in order to achieve superior photolysis rates. In this connection reference is made to the attached publication of S. Bühler et al in Helvetica Chimica Acta, vol 87 (2004, pages 620 to 659). The relevant results of the photolysis rates are summarized on page 631 and the compounds on page 627. As it can be seen in the relevant tables compound 136 (R¹ = phenyl para to the NO₂ group) shows better results than compound 135 (R= phenyl meta to the NO₂ group). Accordingly, for the reasons advanced, the Examiner's position does not appear to be well founded or at least is not consistent with the comparative results presented. Thus, it is applicants' position that the results obtained in the present invention are superior in comparison to the results shown in Pfleiderer et al and could not have been expected so that the present results can not be explained by the Examiner's hindsight reconstruction.

As to the Fodor et al patent, the Examiner states on page 13 of the disclosure that the radical at the top of column 2 of the reference has a photolabile moiety which apparently corresponds to that of the present invention. This is erroneous. In the first place it should be noticed that the radical in column 2 does not contain four different R substituents, but rather three. Secondly, the R³ substituent of the photolabile component of the radical of the reference is not on the phenyl ring of the radical shown, but rather is on the carbon adjacent the carboxy group shown in the compound. Thirdly, the Examiner identifies the R² group of the present claims as corresponding to R³ of the reference. This is incorrect because the critical R² group of the present compound claimed is para to the position of the nitro group on

the phenyl ring, whereas in the photolabile radical of the reference, a methoxy group is in the para position relative to the nitro group which leaves the R¹ and R² groups, which can not be aryl, of the compound of the patent in the ortho and meta positions, respectively, on the phenyl ring relative to the nitro group. Accordingly, the Fodor et al patent shows a methoxy substituent at the same position on the phenyl ring of the radical shown by Pfleiderer et al which is methoxy (or hydrogen) and not aryl. How then does the Fodor et al patent improve upon the deficiencies of Pfleiderer et al?

Claims 1 and 6 stand rejected based on 35 U.S.C. §103(a) as obvious over Pfleiderer et al in view of Fodor et al, U.S. Patent 5,489,678 and further in view of Berlin, DE 19938092. This ground of rejection is respectfully traversed.

Applicants again maintain their position with respect to the Pfleiderer et al and Fodor et al patents as set forth above.

As to the Berlin document, the same discloses a derivatized nucleoside of formula I which is a thiocarbonate compound. It must be noted that phenyl ring of the nucleoside containing the photolabile group has a ring substitution pattern in which group R₅ is para to the nitro group on the phenyl ring. Group R₅ is hydrogen, alkyl or alkoxy or can be a part of a methylenedioxy group along with an adjacent ring carbon atom. The reference simply does not show or suggest that the R₅ group is phenyl (aryl, substituted aryl, heteroaryl or substituted heteroaryl or substituted aroyl), which type of substitution is critical in the present invention. Accordingly, it is clear that the substituents of group R² on the phenyl ring of the present photolabile radical are different and not inclusive of the substituent R⁵ (para position relative to NO₂) on the phenyl ring of the photolabile radical of the reference. Thus, Berlin does not improve upon the deficiencies of the Pfleiderer et al and Fodor et al patents.

Claims 30-32 and 34-46 stand rejected based on 35 U.S.C. §103(a) as obvious over Pfleiderer et al in view of Haugland et al, U.S. Patent 5,635,608. This ground of rejection is respectfully traversed.

Applicants maintain their view stated above with regard to the Pfleiderer et al patent. Further, the Haugland et al patent, in disclosing a photolabile group that can be attached to a nucleoside, does not show a phenethyl type of structure that is bonded through a carbonate group to a nucleoside, but rather a benzyl group. This is a very significant difference. In fact, Haugland et al is basically irrelevant to the present invention since it discloses photolabile compounds that are α -carboxy substituted nitrobenzyl derivatives which are quite different from the nitrophenyl propoxy carbonyl derivatives of the present invention. Furthermore, no indication can be found anywhere in the patent of using phenyl substituents in the para position relative to the NO₂ group. Thus, the Haugland et al patent does not bring the Pfleiderer et al disclosure closer to the present invention. Withdrawal of the rejection is respectfully requested.

Claims 30 and 33 stand rejected based on 35 U.S.C. §103(a) as obvious over Pfleiderer et al in view of Haugland et al, U.S. Patent 5,635,608 and further in view of Berlin. This ground of rejection is respectfully traversed.

Applicants maintain their position with respect to their position as stated above with respect to each of the references. The formulation of the presently claimed photolabile compound is not suggested by the combined patents. Withdrawal of the rejection is respectfully requested.

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Applicants respectfully submit that the above-identified application is in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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